A Review of Health Outcomes in Patients with Psoriasis

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KEYWORDS

• Psoriasis • Treatments • Health outcomes • Resources

Psoriasis is a chronic inflammatory skin disorder that affects 2% to 4% of the United States population.[1] Patients with psoriasis present with scaly and erythematous patches and plaques on the skin.[2] Psoriasis is associated with significant comorbidities and affects patients' quality of life. Successful management of psoriasis patients depends on clinicians' understanding of the various treatment options as well as their recognition of associated comorbidities.

PSORIASIS SUBTYPES

Psoriasis varies greatly in clinical presentation and ranges from mild disease with isolated patches to extensive disease with confluent plaques involving multiple areas of the body. Plaque psoriasis is the most common subtype, affecting 80% to 90% of those with psoriasis.[2] Plaque psoriasis is characterized by erythematous patches or plaques with silvery scales. Other subtypes of psoriasis include guttate, pustular, inverse, and erythrodermic forms. Guttate psoriasis appears as small, drop-shaped lesions on the trunk, limbs, and scalp, and it is sometimes associated with upper respiratory infections.[1] Pustular psoriasis is characterized by multiple pustules on the skin, whereas inverse psoriasis presents with erythematous patches in the intertriginous areas. Erythrodermic psoriasis is characterized by widespread erythema and scaling of the skin.[1]

Measurement of Disease Severity

In clinical practice, psoriasis disease severity is estimated primarily by using the total body surface area (TBSA) involved. Typically, TBSA involvement of less than 2% is considered mild disease, 2% to 10% is moderate disease, and greater than 10% is severe psoriasis. In clinical trials, researchers often use the Psoriasis Area and Severity Index (PASI) to assess disease severity. PASI is a validated disease-severity instrument that integrates area of involvement with erythema, scaling, and induration of psoriatic plaques. PASI ranges from 0 (no disease) to 72 (maximal disease). About 25% to 30% of patients with psoriasis are classified as having moderate-to-severe disease.[3]

Prevalence and Incidence

The National Institute of Arthritis and Musculoskeletal and Skin Diseases estimates that the prevalence of psoriasis in the United States is approximately 4%,[1] whereas psoriasis has a worldwide prevalence of approximately 2% to 3%.[3] Currently, more than 5 million adults have psoriasis, and 260,000 new cases are diagnosed annually in the United States.[4] Psoriasis appears to affect men and women equally. Although psoriasis can affect all age groups, the onset of psoriasis tends to peak between the ages of 20 and 30 and between ages 50 and 60.[1,3] Patients with

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early onset of psoriasis tend to have greater disease severity and a family history of psoriasis.[5]

BURDEN OF PSORIASIS

Impact of Psoriasis on Quality of Life

Psoriasis has a major impact on health-related quality of life that is comparable to other major medical diseases such as cancer, arthritis, hypertension, heart disease, diabetes, and depression.[1,6] In a review of quality-of-life studies from January 1966 to April 2000, investigators found that patients with psoriasis reported physical discomfort, impaired emotional functioning, and negative body image and self-image, as well as limitations in daily activities, social contacts, and work.[6] The severity of the psoriasis was directly correlated to lower levels of quality of life. A population-based survey looking at the association between quality of life and extent of disease showed that nearly 60% of patients with psoriasis report that the disease affects their everyday life and 26% report a change or discontinuation of daily activities.[7]

Economic Burden of Psoriasis

The estimated total direct and indirect health care cost of psoriasis in the United States is 11.25 billion dollars annually, with direct medical costs estimates ranging from 650 million to 4.3 billion dollars.[8,9] The cost of psoriasis in the United States is multidimensional. Total cost includes medical and prescription drug costs, patient expenditures, lost work time, reduced productivity, and diminished quality of life. In a case comparison of 56,528 patients with psoriasis versus the general population, patients with psoriasis had significantly greater health care resource use ($5529 vs $3509), higher total drug use ($1604 vs $822), and greater overall medical costs ($3925 vs $2687).[10]

Psychosocial Burden of Psoriasis

Epidemiologic studies show that the psychosocial burden of psoriasis is one of the most challenging aspects of disease management.[11] Psoriasis affects daily activities of living for nearly 60% of patients, especially in women, younger patients, and those afflicted with moderate-to-severe psoriasis.[7,12] Psychosocial consequences of having psoriasis include decreased self-esteem and stigmatization in social relations and employment. In a questionnaire given to 17,350 patients with psoriasis, as many as two-thirds of patients report that the disease has limited their daily activities in areas such as sleeping, sexual activity, use of hands, walking, sitting for long periods of time, and performing job duties.[13,14]

Owing to visibility of psoriatic lesions, patients with severe psoriasis are especially vulnerable to social stigmatization. Patients have reported being asked to leave hair salons and barbershops, public pools, and health clubs. Compared with patients with psoriasis affecting regions of the body usually covered by clothing, patients with visible plaques that affect hands, arms, and head rate their psoriasis as more disabling.[13,15] Furthermore, the patients' disease severity is directly correlated with lower ratings of self-esteem and a fear of social isolation.[11,14]

This psychological stress from psoriasis can permeate employment and result in financial loss. A two-year study by the National Psoriasis Foundation (NPF) found that having psoriasis is associated with decreased household incomes and reduced employment opportunities, especially for patients with moderate-to-severe disease. Compared with those without psoriasis, psoriasis patients have lower income and are less likely to work full-time. Furthermore, psoriasis was reported as the primary reason for unemployment in 17% of patients with severe psoriasis.[16] An estimated 60% of patients missed an average of 26 days of work each year due to complications of psoriasis.[16]

Psoriasis is also related to decreased sexual intimacy and decreased libido in 30% to 70% of patients.[17,18] In a study conducted by Gupta and Gupta,[17] 40.8% of 120 patients surveyed reported that the disease impacted their sexual activity. The affected group also reported more joint pains, greater area of scaling, and greater pruritus severity. In addition, psoriasis patients had higher depression scores. A recent study has suggested that these comorbidities may contribute to decreased sexual functioning in psoriasis patients.

PSORIASIS COMORBIDITIES

Psoriasis is associated with comorbid conditions, including depression, arthritis, diabetes, hypertension, metabolic syndrome, and cardiovascular events. These comorbid conditions may occur concurrently or years after development of psoriasis.[19,20]

Shared Mechanisms Between Psoriasis and Comorbidities

The presence of rheumatologic and cardiovascular comorbidities among psoriasis patients suggests that a systemic inflammatory process may underlie these disease processes. For example, some studies suggest that increased amounts of pro-inflammatory cytokines, such as tumor necrosis

factor-alpha and interleukin-1, may be linked to depression.[21] Furthermore, psoriasis may predispose patients to increased risk of atherosclerotic disease through a chronic, proinflammatory state that fosters the development of the metabolic syndrome.[22] One proposed mechanism for the association between the formation of atherosclerotic lesions and increased proinflammatory cytokines is that chronic inflammation may lead to increased oxidative modifications of lipoproteins, which are more atherogenic than native lipproteins.[19]

Psychiatric Comorbidity in Psoriasis

Multiple studies have documented higher rates of depression among psoriasis patients compared to control populations.[23–26] Recent studies have shown that psoriasis seems to be an independent risk factor for developing depressive symptoms.[27] Although chronic medical conditions have shown to be associated with depression, the prevalence of active suicidal ideation seemed to be higher in psoriasis patients.[23] Furthermore, a population-based cohort study in the United Kingdom found that psoriasis patients are more likely to be diagnosed with depression, anxiety, or suicidality compared with the general population. Specifically, compared with patients without psoriasis, patients with severe psoriasis have a 72% increased likelihood of having comorbid psychiatric conditions and those with mild psoriasis have a 38% increased likelihood.[26] In addition, young men appeared to be at the highest risk for displaying depression symptoms.

Rheumatologic, Cardiovascular, and Malignancy Comorbidities

Patients with psoriasis have an increased frequency of psoriatic arthritis, cardiovascular diseases, and certain types of malignancies compared with the general population. Psoriatic arthritis affects an estimated 25% to 34% of patients with psoriasis.[28] Although it can develop at any age, psoriatic arthritis most commonly appears approximately 10 years after the onset of psoriasis in most patients.[3] Psoriatic arthritis is characterized by tenderness and swelling of the affected joints. Early diagnosis and treatment are essential in the prevention of progressive joint damage. Although severity of psoriatic arthritis varies greatly, the most severe form of the disease can severely interfere with activities of daily living.[29]

Several epidemiologic studies have suggested an association between cardiovascular diseases and psoriasis.[30–33] In a large population study of patients from the United Kingdom, investigators found that psoriasis conferred an independent risk of myocardial infarctions after adjusting for traditional cardiovascular risk factors. Specifically, the relative risk was found to vary with age and severity of disease. For example, the relative risk of a 30-year-old person with severe psoriasis was 3.1, whereas that for a 60-year-old person with severe disease was 1.36.[34] Increasing epidemiologic evidence suggests that psoriasis may also be associated with diabetes and hypertension.[31,35]

Several studies suggest that psoriasis patients are more likely to have dyslipidemia compared with the general population.[36,37] In these studies, the levels of triglycerides, total cholesterol, low-density lipoprotein, and very-low-density lipoprotein were higher in psoriasis patients compared with the control groups.[36,37] Furthermore, compared with the general population, researchers have found that psoriasis patients are more likely to develop metabolic syndrome, which is characterized by abdominal obesity, elevated cholesterol and triglycerides, elevated blood pressure and insulin resistance, and elevated fasting blood glucose levels.[38] In a 2003 to 2006 cross-sectional health survey of 6546 participants, the prevalence of metabolic syndrome was found to be 40% in the United States among psoriasis patients compared with 23% among controls.[39] The most common presenting feature of metabolic syndrome seen in psoriasis patients was abdominal obesity. Metabolic syndrome confers a threefold to ninefold risk of developing type 2 diabetes and twofold to threefold risk of having an adverse cardiovascular event such as coronary heart disease, stroke, or myocardial infarctions.[40,41]

Studies examining malignancy risks in psoriasis patients are often complicated by the relatively rare occurrence of cancers in this population. Some studies suggest that psoriasis may be associated with increased risk of malignancies, including lymphomas, solid organ tumors, and nonmelanoma skin cancers.[42] In a prospective study of 6905 psoriasis patients that were followed for 9 years, these patients were 1.4 times more likely to develop malignancy compared with the general population.[43] Researchers have speculated that the apparent increased risk of malignancy might be related to psoriasis treatments, among other factors. Notably, the use of psoralen plus ultraviolet A (PUVA) and cyclosporine has been linked to the development of squamous cell carcinoma in psoriasis patients.[44] Previous treatment with retinoids or immunosuppressants also significantly increases the risk of malignancy.[45] In a 15-year prospective study of 1380 patients first

treated with PUVA from 1975 to 1976, the relative risk of malignant melanoma was 1.1 after 15 years and 5.4 after 20 years.[46] The risk was greatest among patients who have had at least 250 PUVA treatments.[46]

Recommendations for Assessment of Comorbidities in Psoriasis

Comorbid conditions in psoriasis are becoming increasingly well recognized in the medical community. The NPF has proposed screening recommendations for dermatologists.[20] NPF recommends that psoriasis be approached as a multisystem disorder that may necessitate referrals to other specialists. Dermatologists are encouraged to inquire about the development of rheumatologic and cardiovascular diseases.[47] Specifically, it is recommended that physicians screen for cardiovascular risk factor according to the American Heart Association (AHA) recommendations. Beginning at age 20, physicians should inquire about risk factors such as family history of coronary heart disease, smoking, alcohol intake, physical activity, and diet. Screening should occur at least every 2 years with measurements of blood pressure, body mass index, waist circumference, and pulse. Measurements of fasting lipids and fasting glucose should be done at least every 5 years, or 2 years if risk factors are present. When patients reach age 40 years, the 10-year risk of developing coronary heart disease should be assessed with a multiple risk factor score every 5 years, or more often if risk factors change. Risk factors used in the global risk assessment includes age, sex, smoking status, systolic blood pressure, and lipid levels.[20]

Lifestyle Changes and Risk Modification

For some psoriasis patients, the large psychosocial burden of the disease may be associated with greater alcohol consumption, smoking, and increased food intake. Alcohol abuse has been linked to a higher incidence and severity of psoriasis, with some studies showing that abstinence from alcohol alone may be associated with psoriasis remission in some patients.[48–51] A recent cross-sectional study by Herron and colleagues[33] found that the prevalence of obesity in patients with psoriasis was higher than that of the general population (34% vs 18%). The prevalence of smoking was also greater (25% vs 9%). Smoking has also been linked with increased psoriasis severity. In a hospital-based cross-section study, smoking more than 20 cigarettes a day was associated with a more than twofold increase in severity of disease.[52,53]

The NPF recommends several lifestyle changes for psoriasis patients. Patients are encouraged to exercise at least three times a week for 20 minutes along with cessation of smoking and moderate alcohol intake.[20] Patients are also encouraged to modify eating habits. For patients already suffering from metabolic syndrome, the AHA guidelines recommend a target body mass index of less than 25, and physical activity for at least 30 minutes each day. Although not officially endorsed by the NPF, participation in psychotherapy or social support groups may help patients with learning disease coping mechanisms and reducing the psychosocial burden. Studies have also shown that, compared with pharmacotherapy alone, psychotherapy can lead to significant reduction in disease severity and psychosocial distress.[54]

TREATMENTS

Treatments for psoriasis need to be tailored to patients based on a variety of factors, including type of psoriasis, disease severity, medical coverage, and access to care. Treatments with topical agents, such as topical steroids and topical vitamin D agents, constitute the first line of therapy for mild-to-moderate disease. However, topical therapy alone is often inadequate for moderate-to-severe psoriasis. For patients with moderate-to-severe disease, phototherapy, systemic therapy, or biologics should be considered. Whereas large body surface area involvement will often necessitate systemic treatments, psoriasis involving critically functioning body regions, such as the hands and feet, sometimes warrant consideration for systemic therapy.[8,55–59]

Defining Treatment Goals

The primary goals in the treatment of psoriasis include reduction of disease severity and improvement of quality of life.[60] Before starting any treatment, dermatologists need to have a detailed discussion with patients regarding chronicity of the disease and help set realistic expectations based on disease severity and selected therapy. Clinicians and patients need to work together to achieve and maintain long-term control of psoriasis while monitoring for adverse effects. Specifically, clinicians need to document changes in psoriasis disease activity at each visit to evaluate effectiveness of treatment. Regular conversations on setting realistic therapeutic goals and encouraging patients to adhere to the treatment regimen are important steps to achieving disease control.

Topical Treatments

Topical treatments are usually considered the first-line therapy for patients with mild psoriasis because of their limited side-effect profiles.[61,62] However, because of the difficulties involved with application to large body surface areas, topical agents are generally used in patients with less than 10% TBSA involvement.[63] Patients with moderate-to-severe psoriasis will often have inadequate response to topical treatments alone, but topical therapy is a useful adjunct to systemic therapy in patients with moderate-to-severe disease.[64]

Corticosteroids are the most commonly prescribed topical agents for their antiinflammatory and antiproliferative properties. These properties are mediated through transcriptional regulation of genes encoding for inflammatory mediators, which leads to downstream inhibition of lymphocyte activation and a reduction in dermal edema and vascular permeability.[65] Topical steroid preparations are available in a variety of potencies; their selection should be based on disease severity, affected body location, and patient preference for vehicles.[66,67] Adverse effects of long-term use of topical corticosteroids include epidermal atrophy, acneiform eruptions, allergic contact dermatitis, and tachyphylaxis. In rare cases, long-term widespread use of high-potency topical steroids is associated with suppression of the hypothalamic-pituitary-adrenal axis.[68] Calcipotriene is a vitamin D3 analog that binds to the keratinocyte receptor and promotes terminal differentiation and inhibition of the proliferation of keratinocytes. Regular use of topical calcipotriene is associated with few adverse effects, such as skin irritation. Few systemic side effects have been reported, but rare cases of hypercalcemia have been reported in patients who use excess quantities for a significant period.[69] As monotherapy, the efficacy of calcipotriene is thought to be similar to that of a class two or three topical corticosteroid, and its efficacy improves significantly when used in combination with certain types of high-potency topical steroids.

Topical retinoids, such as tazarotene, are vitamin A derivatives that selectively bind to retinoic acid receptors. Retinoids are thought to exert their effects by modulating the cellular differentiation of the epidermis, which results in decreased scaling, erythema, and thickness of the plaques.[70] Topical retinoids have a slower onset of action compared with high potency corticosteroids; however, their use as a monotherapy resulted in an excellent response or complete clearing of target lesions, as evaluated by the investigators, in 70% of patients treated for 3 months in one clinical study.[71] Adverse side effects of topical retinoids include irritation, burning, itching, stinging, and erythema, and they can occur in 20% to 40% of patients. Of note, tazarotene is labeled as pregnancy category X and, therefore, it should not be used in women of childbearing age.

Other topical agents include tacrolimus, salicylic acid, and emollients. Tacrolimus is a calcineurin inhibitor and functions as an immunosuppressant. Initial studies did not demonstrate significant efficacy of topical tacrolimus in treating plaque-type psoriasis, which may be related to poor penetration of the active ingredients into thick psoriatic plaques.[72–74] However, tacrolimus seems to be modestly efficacious in treating areas where skin is thinner, such as in the face and groin areas.[75] Salicylic acid is commonly used in combination with corticosteroids to improve penetration of topical steroids. Emollients are used to relieve dryness, scaling, and pruritus.

Phototherapy

Phototherapy has been used for decades to treat generalized psoriasis. PUVA and UV-B are effective in achieving significant clearance of psoriatic lesions. A main contraindication of phototherapy is having a photosensitive skin disease, such as lupus erythematosus.

PUVA phototherapy consists of emission of UVA wavelengths (320–400 nm) after patients have ingested psoralen. Compared with UV-B, PUVA penetrates deeper into the skin because of its longer wavelengths. Patients undergoing PUVA therapy require fewer treatment sessions than UV-B phototherapy to achieve clearance. However, PUVA is associated with greater short-term and long-term adverse effects. Short-term adverse reactions of PUVA include nausea, headache, depression, hyperkinesis, and phototoxicity. Long-term use of PUVA is associated with significant photoaging and an increased risk of squamous cell carcinomas and melanomas in patients exposed to high cumulative doses.[46,76–79] PUVA can be combined with other topical and systemic treatments to achieve greater clearance. Specifically, combination PUVA-acitretin regimen seems to reduce the risk of cutaneous malignancy through reduced number of phototherapy sessions and, thereby, lower cumulative dose.[80]

Broadband UV-B therapy (290–320 nm) remains one of the mainstay treatments for moderate-to-severe psoriasis. Broadband UV-B therapy can be combined with other topical and systemic therapies to improve patient response. A recent literature review of studies on the use of UV-B phototherapy for psoriasis from 1966 to 2002 found no increased incidence of skin cancer risk

with the use of monotherapy or combined UV-B phototherapy.[81] The most important contributing factor to skin cancer seemed to be prior exposure to ionizing radiation.[82]

Narrowband UV-B is another subtype of UV-B phototherapy that consists of specific wavelengths in the range of 311 to 313 nm. Narrowband UV-B is effective in treating moderate-to-severe psoriasis while limiting wavelengths responsible for premature aging and burning. In a studying comparing narrow to broadband UV-B, narrowband seems to achieve greater clearance of psoriatic lesions but often with longer treatment periods.[83]

Oral Systemic Agents

Common oral agents used in the treatment of moderate-to-severe psoriasis include methotrexate, acitretin, and cyclosporine. These agents are effective in achieving initial clearance as well as long-term maintenance therapy. However, adverse effects of these agents must be carefully considered and monitored during treatment.

Methotrexate inhibits DNA synthesis, thereby directly inhibiting epidermal cell proliferation and slowing cell turnover rates. Methotrexate is effective in treating various subtypes of psoriasis, including plaque-type, erythrodermic, and pustular psoriasis as well as psoriatic arthritis. Adverse effects of methotrexate include bone marrow suppression, pneumonitis, infectious complications, and spontaneous abortion.[84] Preexisting liver and kidney diseases may enhance methotrexate toxicity. Liver and kidney function tests need to be obtained before the initiation of therapy as well as during therapy. The incidence of liver failure and cirrhosis can range from 3% with cumulative doses in the range of 1.5 to 2 g to as high as 26% with a cumulative dose of 4 g.[85] The risks of hepatotoxicity are greatest among those who are obese, have a history of viral hepatitis or diabetes, and have heavy alcohol consumption.[86]

Systemic retinoids, such as acitretin, modulate the cellular differentiation of the epidermis and lead to reduced scaling, erythema, and thickness of psoriatic plaques.[70] Acitretin can be used as a monotherapy or in combination with other agents to increase treatment efficacy. Acitretin is classified as pregnancy category X and can be associated with liver function test abnormalities in as many as 25& to 30% of patients, especially in those on high-dose therapy.[87] Of note, acitretin remains the only systemic therapy that is not immunosuppressive and, as such, it can be considered in patients with comorbid chronic conditions such as HIV and hepatitis B and C, with appropriate monitoring of liver function tests.

Cyclosporine is usually reserved for short-term, rapid control of psoriasis flares. Most studies recommend that the duration of cyclosporine administration not exceed 1 year.[88–91] Short-term use of cyclosporine is associated with side effects such as nausea, headache, malaise, and tremor that resolve in weeks to months. Long-term use is associated with adverse effects such as impaired kidney function, hypertension, hyperlipidemia, elevated creatinine, and elevated urea nitrogen. Cyclosporine is classified as pregnancy category B by the US Food and Drug Administration.

Biologic Therapy

Biologic treatments in psoriasis typically act through immunomodulation. To date, several classes of biologics exist for psoriasis treatment, including anti-tumor necrosis factor (anti-TNF) agents, anti-T cell agents, and anti-IL12/23p40 agents. TNF is a key pro-inflammatory cytokine involved in the pathogenesis of psoriasis. Tumor necrosis factor (TNF) levels have been found to be higher in psoriatic lesions compared with nonlesional skin.[92] Among the anti-TNF agents, etanercept is a dimeric fusion protein that joins the extracellular ligand-binding domain of human TNF receptor with the Fc component of the IgG1. Etanercept binds and inhibits TNF activity, thereby inhibiting downstream inflammatory events. Studies have suggested that etanercept has greater affinity for TNF than the endogenous receptors.[93]

Adalimumab is another member of the anti-TNF family; it is a fully humanized anti-TNF monoclonal IgG1 antibody that prevents binding of TNF to its receptor. Adalimumab has been found to be effective in the treatment of moderate-to-severe psoriasis in phase III trials.[94] Specifically, after the first 16 weeks of treatment, 71% of patients receiving adalimumab achieved greater than 75% improvement in PASI score, compared with 7% of patients receiving placebo.[94]

Infliximab is a chimeric anti-TNF monoclonal IgG antibody. It consists of both mouse and human constant and variable regions. It is able to bind with high affinity and specificity to membrane-bound TNF. The infliximab-TNF complex has a higher binding affinity than the etanercept-TNF complex.[95] A meta-analysis of reviews published on psoriasis from 2007 to 2008 found that, among biologic agents, infliximab is highly effective in achieving 75% reduction in the PASI in moderate-to-severe psoriasis after 10 to 14 weeks of treatment.[57]

Contraindications to the use of anti-TNF biologics include active, serious, and recurrent infections; active tuberculosis; history of demyelinating disease; or congestive heart failure.[92,96] Rarely,

TNF inhibitors have been associated with more severe systemic complications, such as congestive heart failure, cytopenia, increased liver function tests, malignancy, lupus-like syndrome, thrombocytopenia, and demyelinating disorders, although their role in these diseases is not fully understood.[97] However, a recent analysis of the safety of tumor necrosis factor antagonists found that, during the initial year of treatment, the rate of success with anti-TNF therapy was at least two orders of magnitude greater than the likelihood of serious toxicity.[98]

Another class of biologics is directed specifically against T-cells. Alefacept is an antibody that blocks the interaction between costimulatory molecules leukocyte function antigen-3 (LFA-3) and CD2. Inhibition of binding between LFA3 and CD2 mitigates T cell response.[92] Alefacept selectively inhibits the memory-effector T cells, which compose more than 75% of the T cells found in psoriatic plaques.[92] Controlled studies have shown that alefacept was associated with significant improvements in PASI. Specifically, the mean reductions in PASI in the 15 mg alefacept, 10 mg alefacept, and placebo were 46%, 41%, and 25%, respectively.[99] Although side effects are generally mild and well-tolerated, alefacept has been associated with reduced immunity. Because of its mechanism of action, alefacept can cause a dose-dependent reduction in the total number of circulating lymphocytes, which places the patient at greater risk for infection, such as upper respiratory infections and the common cold.[100]

Ustekinumab is a monoclonal antibody directed against the p40 subunit of IL12 and IL23. Specifically, ustekinumab binds with high affinity to the p40 subunit common to both IL12 and IL23. In a 12-week comparison study of ustekinumab (45 mg or 90 mg) and high-dose etanercept (50 mg twice weekly) for moderate-to-severe psoriasis, ustekinumab was found to have statistically significant greater efficacy.[101] As with all currently available biologics for the treatment of psoriasis, although safety data beyond 3 years have not been reported with ustekinumab, clinicians need to exercise caution when prescribing ustekinumab to immunosuppressed patients and those with a history of malignancy.[102] Common adverse effects include nasopharyngitis, upper respiratory tract infections, and headaches.

Combination Therapy

Combination therapy has been used to increase efficacy and minimize toxicity by leveraging synergism among different medications. Combination therapy may also be necessary when a single agent is insufficient to adequately control disease severity.

Phototherapy is often used in combination with oral retinoids, such as acitretin, to decrease the total amount of phototherapy sessions necessary to achieve clearance.[103–105] A retrospective study of 40 patients with recalcitrant plaque psoriasis treated with a combination of acitretin and broad-band UV-B three times a week resulted in at least 75% improvements in 29 of the patients examined.[106] A randomized, double-blinded comparison of PUVA with and without acitretin found that 96% of patients receiving combination therapy (PUVA and acitretin) achieved complete or near clearance of psoriasis compared with 80% of patients who received PUVA alone ($P<.05$).[107] The side-effect profiles were also favorable with combination therapy because the cumulative dose of administered PUVA was 42% less with combination therapy compared with monotherapy with PUVA.

Certain combinations of topical therapies have been developed with the goal of achieving greater synergistic efficacy than either agent alone achieves. For example, the efficacy of calcipotriene is enhanced when used in combination with a selected number of agents. In a randomized, double-blinded, phase III clinical trial examining the combined use of calcipotriene with betamethasone compared with monotherapy of each component, the combination of calcipotriene and betamethasone resulted in PASI of 65% to 72% compared with a PASI of 46% to 57% in patients treated with monotherapy alone.[108] A separate study examining combination calcipotriol and acitretin found that 40% of patients achieved complete clearance with the combination therapy compared with 15% in the acitretin monotherapy group after 12 weeks.[109]

Economic Considerations of Treatment Costs

The costs of health care and medications for the treatment of psoriasis continue to climb for patients and society at-large. One study estimated that outpatient cost for treating psoriasis ranged from $1400 to $6000 per year.[4] A 2008 study comparing direct medical costs of 12,280 patients with psoriasis to 36,840 control participants showed that psoriatic patients spend $366 more per month in medical costs compared with the control population.[8] Pearce and colleagues[110] examined the cost-effectiveness of psoriasis treatments over a 12-week period comparing methotrexate, acitretin, cyclosporine, narrow band UV-B, PUVA, etanercept, and efalizumab. The total

cost per completed treatment regimen was calculated based on drug acquisition costs, dosing and cost of physician visits, laboratory testing, phototherapy treatment charges, liver biopsy, and infusions charges. The total cost for a 12-week completed treatment was $3921 for PUVA, $2658 for UV-B, $436 for methotrexate, $1419 for acitretin, $2464 for cyclosporine, $4299 for efalizumab, and $7993 for etanercept. The cost-effectiveness for a 12-week completed treatment was $623 for methotrexate, $2729 for acitretin, $3692 for narrow band UV-B, $4668 for PUVA, $16,323 for etanercept, and $17,196 for efalizumab.[110]

SERVICES AVAILABLE

National Resources

Patients with psoriasis and their families can seek educational resources, along with support and advocacy groups, from a variety of national resource organizations. Online educational resources exist on Web sites from the American Academy of Dermatology (www.aad.org), the National Psoriasis Foundation (www.psoarisis.org), and the National Institute of Arthritis and Musculoskeletal and Skin Diseases (www.niams.nih.gov). Psoriasis Cure Now! is a nonprofit patient advocacy group aimed to increase federal funding for psoriasis research and increase access to safe, effective treatments for all psoriasis patients.

One challenge for many psoriasis patients who are uninsured or underinsured is gaining access to the wide range of available treatments. Patients who need assistance on learning how to obtain insurance approval or health care access can find helpful information at Patient Advocate Foundation (www.patientadvocate.org). For patients interested in helping to advance research in psoriasis, patients can search the Web site of the US National Institutes of Health for clinical research studies on psoriasis and psoriatic arthritis (http://clinicaltrials.gov).

Primary Care and Specialty Care of Psoriasis Patients

A recent survey found that psoriasis was more likely to be diagnosed by a dermatologist than by a primary care physician.[111] Eighty-five percent of patients with mild psoriasis were diagnosed during an initial visit with the dermatologist compared with 55% initially seen by a primary care physician. In comparison, 78% and 60% of patients with moderate-to-severe psoriasis were diagnosed by dermatologists and primary care physicians, respectively.[111] Referral to dermatologists need to be considered for patients who had unsatisfactory treatment response to topical therapy, greater than 10% affected TBSA, presence of pustular lesions, and are candidates for systemic therapy.[112] Patients with moderate-to-severe psoriasis will likely benefit from a multidisciplinary team of dermatologists and other physicians for management of psoriasis and associated co-morbid conditions.

SUMMARY

As basic and translational research efforts continue to expand, researchers are developing novel agents to treat psoriasis, especially for those with moderate-to-severe disease. However, access and affordability of current treatments often present a challenge for segments of the patient population, such as those who are uninsured or underinsured. As previously discussed, the average cost of outpatient treatment can range from $1600 to $6000 per year, which can be prohibitively high for patients without a comprehensive insurance plan.[4] For patients with moderate-to-severe psoriasis who would benefit from biologic therapy, costs often influence the therapeutic decision-making process.[110] Advocacy groups, such as Psoriasis Cure Now!, are working to increase access to safe, effective treatments for all psoriasis patients. The pharmaceutical industry, which produces biologic agents, has begun concerted efforts to offer programs for drug access for underinsured patients. Continued efforts to reduce treatment disparity are necessary in the coming years.

As our understanding of psoriasis evolve from a skin-limited condition to a systemic condition, greater research efforts are necessary in the dermatoepidemiology of psoriasis. Specifically, exploring psoriasis comorbidities will have significant implications on improving the overall health status of psoriasis patients. Although literature is growing on the association between psoriasis and cardiovascular, rheumatologic, and psychiatric comorbidities, we will need to dissect the degree to which these comorbid conditions interact with psoriasis disease process. Future translational research will be necessary to understand common pathophysiological mechanisms that underlie psoriasis and its comorbidities.

In addition to elucidating which comorbid conditions are associated with psoriasis, increased clinical and translational research efforts may be directed at (1) predicting the development of comorbid conditions, and (2) whether systemic treatment of psoriasis impact health outcomes of comorbid conditions. This scrupulous approach to translational and clinical research will allow us to improve overall wellbeing of psoriasis patients.

List of Acronyms

AAD	American Academy of Dermatology
AHA	American Heart Association
CD2	Cluster of differentiation 2
FDA	US Food and Drug Administration
HPA	Hypothalamic-pituitary-adrenal axis
HRQoL	Health-related quality of life
IL12	Interleukin 12
LFA-3	Leukocyte function antigen 3
MI	Myocardial infarction
NAIMS	National Institute of Arthritis and Musculoskeletal and Skin Diseases
NBUVB	Narrow band ultraviolet B
NPF	National Psoriasis Foundation
PASI	Psoriasis Area and Severity Index
PASI75	75% Reduction in the Psoriasis Area and Severity Index
PUVA	Psoralen plus ultraviolet A
RR	Relative risk
TBSA	Total body surface area
TNF	Tumor-necrosis factor
UVB	Ultraviolet B

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